

PCT

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国際事務局

## 特許協力条約に基づいて公開された国際出願



(51) 国際特許分類6 C12Q 1/68, C12N 15/11, C12M 1/32, G01N 33/58	A1	(11) 国際公開番号 WO99/06591  (43) 国際公開日 1999年2月11日(11.02.99)
(21) 国際出願番号 PCT/JP98/03413		
(22) 国際出願日 1998年7月30日(30.07.98)		
(30) 優先権データ 特願平9/206602	1997年7月31日(31.07.97) JP	(81) 指定国 CA, JP, US, 歐州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). 添付公開書類 国際調査報告書
(71) 出願人 (米国を除くすべての指定国について) 理化学研究所( THE INSTITUTE OF PHYSICAL AND CHEMICAL RESEARCH)[JP/JP] 〒351-0198 埼玉県和光市広沢2番1号 Saitama, (JP)		
(71) 出願人 ; および (72) 発明者 林崎良英(HAYASHIZAKI, Yoshihide)[JP/JP] 〒305-0074 茨城県つくば市高野台三丁目1-1 理化学研究所 ライフサイエンス筑波研究センター内 Ibaraki, (JP)		
(74) 代理人 弁理士 塩澤寿夫, 外(SHIOZAWA, Hisao et al.) 〒104-0031 東京都中央区京橋一丁目5番5号 KRFビル5階 Tokyo, (JP)		

(54)Title: METHODS FOR DETECTING MUTATION IN BASE SEQUENCE

(54)発明の名称 塩基配列中の変異を検出する方法

## (57) Abstract

A method for detecting a mutated nucleic acid and/or DNA fragment which comprises hybridizing a nucleic acid fragment, etc. immobilized on a plate with another nucleic acid fragment, etc. to be examined in the presence of the mutation, binding the thus formed inappropriate base pair to a substance capable of binding specifically to the inappropriate base pair, such as labeled Mut S, and then detecting and identifying the fragment to which the above substance has been bound; a method which comprises treating, in place of the above substance capable of binding specifically to the inappropriate pair, an inappropriate base pair formed between hybridized fragments with a substance capable of specifically recognizing and cleaving the inappropriate base pair, thus cleaving or removing the hybridized fragment starting with the inappropriate base pair, labeling the fragment remaining on a plate after the cleavage or removal, and then detecting and identifying the thus labeled fragment; and substances capable of binding specifically to an inappropriate base pair such as GFP-labeled Mut S. Thus, structural mutations in two or more genes can be detected in parallel. In particular, structural mutations can be detected while monitoring the extent of expression simultaneously.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/03413

A. CLASSIFICATION OF SUBJECT MATTER  
Int.Cl<sup>6</sup> C12Q1/68, C12N15/11, C12M1/32, G01N33/58

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl<sup>6</sup> C12Q1/68, C12N15/11-15/62, C12M1/00-1/42

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
BIOSIS (DIALOG), WPI (DIALOG), CA (STN)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X/Y/A	JP, 7-500493, A (Upstate Biotechnology, Inc.), 19 January, 1995 (19. 01. 95) & WO, 93/02116, A1 & EP, 596028, A1	1-4, 19-25, 27/5, 26/ 6-18, 28-30
X/Y/A	JP, 7-327698, A (SRL Inc.), 19 December, 1995 (19. 12. 95) (Family: none)	1-4, 19-25, 27/5, 26/ 6-18, 28-30
P, X	WO, 97/45555, A1 (PHARMACIA BIOTECH AB), 4 December, 1997 (04. 12. 97) (Family: none)	1-4, 19-25, 27
Y	Science, Volume 263, issued 11 February 1994, Martin Chalfie et al., "Green Fluorescent Protein as a Marker for Gene Expression", pages 802-805	5, 26
A	Cold Spring Harbor Symposia on Quantitative Biology, Volume 51, issued 1986, R.M. Myers and T. Maniatis, "Recent Advances in the Development of Methods for Detecting Single-base Substitutions Associated with Human Genetic Diseases", pages 275-284	9-22

 Further documents are listed in the continuation of Box C.  See patent family annex.

- \* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search  
27 October, 1998 (27. 10. 98)Date of mailing of the international search report  
10 November, 1998 (10. 11. 98)Name and mailing address of the ISA/  
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/03413

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Genomics, Volume 14, issued 1992, A-Lien Lu and Ih-Chang Hsu, "Detection of Single DNA Base Mutations with Mismatch Repair Enzymes", pages 249-255	9-22
A	Science, Volume 236, issued 17 April 1987, Richard A. Gibbs and C. Thomas Caskey, "Identification and Localization of Mutations at the Lesch-Nyhan Locus by Ribonuclease A Cleavage", pages 303-305	9-22
Y	Proceedings of the National Academy of Sciences of the United States of America, Volume 93, issued October 1996, Mark Schena et al., "Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes", pages 10614-10619	28-30
Y	JP, 60-61594, A (Joel Proesler et al.), 9 April, 1985 (09. 04. 85) (Family: none)	28-30
A	JP, 9-504699, A (Gene Check, Inc.), 13 May, 1997 (13. 05. 97) & WO, 95/12689, A1 & EP, 733126, A1	1-30
A	WO, 95/29258, A1 (ST. JAMES' AND SEACROFT UNIVERSITY HOSPITALS NHS TRUST), 2 November, 1995 (02. 11. 95) & EP, 758402, A1	1-30
A	Mutation Research, Volume 374, Number 2, issued 21 March 1997, Barbara L. Parsons and Robert H. Heflich, "Evaluation of MutS as a tool for direct measurement of point mutations in genomic DNA", pages 277-285	1-30

## PATENT COOPERATION TREATY

PCT

**NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SHIOZAWA, Hisao  
KRF Building  
5th Floor  
5-5, Kyobashi 1-chome  
Chuo-ku  
Tokyo 104-0031  
JAPON

**RECEIVED**

1998.10. - 1

SHIOZAWA, IMAMURA  
& KAMATA

Date of mailing (day/month/year) 22 September 1998 (22.09.98)
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Applicant's or agent's file reference 98585H	<b>IMPORTANT NOTIFICATION</b>
International application No. PCT/JP98/03413	International filing date (day/month/year) 30 July 1998 (30.07.98)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 31 July 1997 (31.07.97)

Applicant <b>THE INSTITUTE OF PHYSICAL AND CHEMICAL RESEARCH et al</b>
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1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
31 July 1997 (31.07.97)	9/206602	JP	21 Sept 1998 (21.09.98)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No. (41-22) 740.14.35	Authorized officer  K. Takeda  Telephone No. (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

**NOTIFICATION OF RECEIPT OF  
RECORD COPY**  
(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

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SHIOZAWA, Hisao  
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5-5, Kyobashi 1-chome  
Chuo-ku  
Tokyo 104-0031  
JAPON

**RECEIVED**

1998, 9, - 7

SHIOZAWA, IMAMURA  
& KAMATA

Date of mailing (day/month/year) 17 August 1998 (17.08.98)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference 98585H	International application No. PCT/JP98/03413

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

THE INSTITUTE OF PHYSICAL AND CHEMICAL RESEARCH (for all designated States except US)

HAYASHIZAKI, Yoshihide (for US)

International filing date : 30 July 1998 (30.07.98)  
Priority date(s) claimed : 31 July 1997 (31.07.97)  
Date of receipt of the record copy by the International Bureau : 14 August 1998 (14.08.98)  
List of designated Offices :

EP : AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE  
National : CA,JP,US

### ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- time limits for entry into the national phase
- confirmation of precautionary designations
- requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No. (41-22) 740.14.35	Authorized officer:  M. Sakai
	Telephone No. (41-22) 338.83.38

**INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE**

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

**CONFIRMATION OF PRECAUTIONARY DESIGNATIONS**

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

**REQUIREMENTS REGARDING PRIORITY DOCUMENTS**

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/JP98/03413

International Application No.

International Filing Date July 30, 1998

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) 98585H

### Box No. I TITLE OF INVENTION

Method for Detecting Mutations in Nucleotide Sequences

### Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

The Institute of Physical and Chemical Research

2-1, Hirosawa, Wako-shi, Saitama 351-0198  
Japan

This person is also inventor.

Telephone No.  
048-462-1111

Faxsimile No.  
048-462-4609

Teleprinter No.

State (that is, country) of nationality:

JAPAN

State (that is, country) of residence:

JAPAN

This person is applicant for the purposes of:  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box

### Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

HAYASHIZAKI Yoshihide

c/o The Institute of Physical and Chemical Research, Tsukuba Life Science Center  
1-1, Koyadai 3-chome, Tsukuba-shi, Ibaraki  
305-0074 JAPAN

This person is:

applicant only

applicant and inventor

inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

JAPAN

State (that is, country) of residence:

JAPAN

This person is applicant for the purposes of:  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated on a continuation sheet.

### Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

agent

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

9263 Patent Attorney, SHIOZAWA Hisao  
9621 Patent Attorney, IMAMURA Masazumi  
9584 Patent Attorney, KAMATA Junji

5th Floor, KRF Bldg., 5-5, Kyobashi 1-chome,  
Chuo-ku, Tokyo 104-0031 JAPAN

Telephone No.

03-3271-1331

Faxsimile No.

03-3271-1410

Teleprinter No.

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**Box No.V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) (*mark the applicable check-boxes; at least one must be marked*):

**Regional Patent**

- AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (*if other kind of protection or treatment desired, specify on dotted line*) .....

**National Patent (if other kind of protection or treatment desired, specify on dotted line):**

- |   |   |
|---|---|
| <input type="checkbox"/> AL Albania .....                               | <input type="checkbox"/> LS Lesotho .....                                   |
| <input type="checkbox"/> AM Armenia .....                               | <input type="checkbox"/> LT Lithuania .....                                 |
| <input type="checkbox"/> AT Austria .....                               | <input type="checkbox"/> LU Luxembourg .....                                |
| <input type="checkbox"/> AU Australia .....                             | <input type="checkbox"/> LV Latvia .....                                    |
| <input type="checkbox"/> AZ Azerbaijan .....                            | <input type="checkbox"/> MD Republic of Moldova .....                       |
| <input type="checkbox"/> BA Bosnia and Herzegovina .....                | <input type="checkbox"/> MG Madagascar .....                                |
| <input type="checkbox"/> BB Barbados .....                              | <input type="checkbox"/> MK The former Yugoslav Republic of Macedonia ..... |
| <input type="checkbox"/> BG Bulgaria .....                              | <input type="checkbox"/> .....  |
| <input type="checkbox"/> BR Brazil .....                                | <input type="checkbox"/> MN Mongolia .....                                  |
| <input type="checkbox"/> BY Belarus .....                               | <input type="checkbox"/> MW Malawi .....                                    |
| <input checked="" type="checkbox"/> CA Canada .....                     | <input type="checkbox"/> MX Mexico .....                                    |
| <input type="checkbox"/> CH and LI Switzerland and Liechtenstein .....  | <input type="checkbox"/> NO Norway .....                                    |
| <input type="checkbox"/> CN China .....                                 | <input type="checkbox"/> NZ New Zealand .....                               |
| <input type="checkbox"/> CU Cuba .....                                  | <input type="checkbox"/> PL Poland .....                                    |
| <input type="checkbox"/> CZ Czech Republic .....                        | <input type="checkbox"/> PT Portugal .....                                  |
| <input type="checkbox"/> DE Germany .....                               | <input type="checkbox"/> RO Romania .....                                   |
| <input type="checkbox"/> DK Denmark .....                               | <input type="checkbox"/> RU Russian Federation .....                        |
| <input type="checkbox"/> EE Estonia .....                               | <input type="checkbox"/> SD Sudan .....                                     |
| <input type="checkbox"/> ES Spain .....                                 | <input type="checkbox"/> SE Sweden .....                                    |
| <input type="checkbox"/> FI Finland .....                               | <input type="checkbox"/> SG Singapore .....                                 |
| <input type="checkbox"/> GB United Kingdom .....                        | <input type="checkbox"/> SI Slovenia .....                                  |
| <input type="checkbox"/> GE Georgia .....                               | <input type="checkbox"/> SK Slovakia .....                                  |
| <input type="checkbox"/> GH Ghana .....                                 | <input type="checkbox"/> SL Sierra Leone .....                              |
| <input type="checkbox"/> GM Gambia .....                                | <input type="checkbox"/> TJ Tajikistan .....                                |
| <input type="checkbox"/> GW Guinea-Bissau .....                         | <input type="checkbox"/> TM Turkmenistan .....                              |
| <input type="checkbox"/> HR Croatia .....                               | <input type="checkbox"/> TR Turkey .....                                    |
| <input type="checkbox"/> HU Hungary .....                               | <input type="checkbox"/> TT Trinidad and Tobago .....                       |
| <input type="checkbox"/> ID Indonesia .....                             | <input type="checkbox"/> UA Ukraine .....                                   |
| <input type="checkbox"/> IL Israel .....                                | <input type="checkbox"/> UG Uganda .....                                    |
| <input type="checkbox"/> IS Iceland .....                               | <input checked="" type="checkbox"/> US United States of America .....       |
| <input checked="" type="checkbox"/> JP Japan .....                      | <input type="checkbox"/> .....  |
| <input type="checkbox"/> KE Kenya .....                                 | <input type="checkbox"/> .....  |
| <input type="checkbox"/> KG Kyrgyzstan .....                            | <input type="checkbox"/> .....  |
| <input type="checkbox"/> KP Democratic People's Republic of Korea ..... | <input type="checkbox"/> .....  |
| <input type="checkbox"/> KR Republic of Korea .....                     | <input type="checkbox"/> .....  |
| <input type="checkbox"/> KZ Kazakhstan .....                            | <input type="checkbox"/> .....  |
| <input type="checkbox"/> LC Saint Lucia .....                           | <input type="checkbox"/> .....  |
| <input type="checkbox"/> LK Sri Lanka .....                             | <input type="checkbox"/> .....  |
| <input type="checkbox"/> LR Liberia .....                               | <input type="checkbox"/> .....  |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- .....
- .....

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (*Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.*)

**Box No. VI PRIORITY CLAIM**Further priority claims are indicated in the Supplemental Box 

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) Japan	31/07/97	Patent Application 9-206602	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : (1)

**Box No. VII INTERNATIONAL SEARCHING AUTHORITY**

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / JP

Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:

Country (or regional Office): Date (day/month/year): Number:

**Box No. VIII CHECK LIST**

This international application contains the following number of sheets:

- |                  |    |        |
|------------------|----|--------|
| 1. request :     | 3  | sheets |
| 2. description : | 19 | sheets |
| 3. claims :      | 4  | sheets |
| 4. abstract :    | 1  | sheets |
| 5. drawings :    | 2  | sheets |
| Total :          | 29 | sheets |

This international application is accompanied by the item(s) marked below:

- |   |  |
|---|--|
| 1. <input type="checkbox"/> separate signed power of attorney                         | 5. <input checked="" type="checkbox"/> fee calculation sheet   |
| 2. <input type="checkbox"/> copy of general power of attorney                         | 6. <input type="checkbox"/> separate indications concerning deposited microorganisms                 |
| 3. <input type="checkbox"/> statement explaining lack of signature                    | 7. <input type="checkbox"/> nucleotide and/or amino acid sequence listing (diskette)                 |
| 4. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): | 8. <input checked="" type="checkbox"/> other (specify): Request for transmittal of priority document |

Figure No. \_\_\_\_\_ of the drawings (if any) should accompany the abstract when it is published.

**Box No. IX SIGNATURE OF APPLICANT OR AGENT**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

IMAMURA Masazumi

SHIOZAWA Hisao

KAMATA Junji

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority ISA / JP	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid

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Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

# PCT

## FEE CALCULATION SHEET Annex to the Request

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International application No.

Applicant's or agent's  
file reference

98585H

Date stamp of the receiving Office

Applicant

The Institute of Physical and Chemical Research

### CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . T
2. SEARCH FEE . . . . . S  
International search to be carried out by \_\_\_\_\_ 95,000 (T+S)  
*(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)*
3. INTERNATIONAL FEE  
**Basic Fee**  
The international application contains 29 sheets.  
first 30 sheets . . . . . 55,000 b1  
$$0 \times 1,300 = 0 \quad \text{b2}$$
 remaining sheets additional amount  
Add amounts entered at b1 and b2 and enter total at B . . . . . 55,000 B
- Designation Fees  
The international application contains 4 designations.  
$$4 \times 12,700 = 50,800 \quad \text{D}$$
 number of designation fees amount of designation fee payable (maximum 11)
- Add amounts entered at B and D and enter total at I . . . . . 105,800 I  
*(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)*
4. FEE FOR PRIORITY DOCUMENT (if applicable) . . . . . P
5. TOTAL FEES PAYABLE . . . . . 200,800 TOTAL  
Add amounts entered at T, S, I and P, and enter total in the TOTAL box

The designation fees are not paid at this time.

### MODE OF PAYMENT

- |  |   |   |
|--|---|---|
| <input type="checkbox"/> authorization to charge deposit account (see below) | <input type="checkbox"/> bank draft     | <input type="checkbox"/> coupons                |
| <input type="checkbox"/> cheque  | <input type="checkbox"/> cash           | <input type="checkbox"/> other (specify): _____ |
| <input type="checkbox"/> postal money order                                  | <input type="checkbox"/> revenue stamps |   |

### DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

- The RO/  is hereby authorized to charge the total fees indicated above to my deposit account.
- is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No.

Date (day/month/year)

Signature

E P U S

P C T

## 特許協力条約

## 国際調査報告

(法8条、法施行規則第40、41条)  
[PCT18条、PCT規則43、44]

出願人又は代理人 の書類記号	98585H	今後の手続きについては、国際調査報告の送付通知様式(PCT/ISA/220)及び下記5を参照すること。	
国際出願番号	PCT/JP98/03413	国際出願日 (日.月.年)	30.07.98 優先日 (日.月.年)
出願人(氏名又は名称)	理化研究所		

国際調査機関が作成したこの国際調査報告を法施行規則第41条(PCT18条)の規定に従い出願人に送付する。  
この写しは国際事務局にも送付される。

この国際調査報告は、全部で 3 ページである。

- この調査報告に引用された先行技術文献の写しも添付されている。
1.  請求の範囲の一部の調査ができない(第I欄参照)。
2.  発明の単一性が欠如している(第II欄参照)。
3.  この国際出願は、ヌクレオチド及び/又はアミノ酸配列リストを含んでおり、次の配列リストに基づき国際調査を行った。
  - この国際出願と共に提出されたもの
  - 出願人がこの国際出願とは別に提出したもの
    - しかし、出願時の国際出願の開示の範囲を越える事項を含まない旨を記載した書面が添付されていない
    - この国際調査機関が書換えたもの
4. 発明の名称は  出願人が提出したものを承認する。  
 次に示すように国際調査機関が作成した。
- 
5. 要約は  出願人が提出したものを承認する。  
 第III欄に示されているように、法施行規則第47条(PCT規則38.2(b))の規定により国際調査機関が作成した。出願人は、この国際調査報告の発送の日から1カ月以内にこの国際調査機関に意見を提出することができる。
6. 要約書とともに公表される図は、  
 第\_\_\_\_\_図とする。  出願人が示したとおりである.  なし  
 出願人は図を示さなかった。  
 本図は発明の特徴を一層よく表している。

## A. 発明の属する分野の分類(国際特許分類(IPC))

Int.Cl<sup>6</sup> C12Q1/68, C12N15/11, C12M1/32, G01N33/58

## B. 調査を行った分野

調査を行った最小限資料(国際特許分類(IPC))

Int.Cl<sup>6</sup> C12Q1/68, C12N15/11-15/62, C12M1/00-1/42

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース(データベースの名称、調査に使用した用語)

BIOSIS(DIALOG), WPI(DIALOG), CA(STN)

## C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
X/Y/A	JP, 7-500493, A (アプステイト・バイオテクノロジー・インコーポレーテッド) 19.1月.1995 (19.01.95) & WO, 93/02116, A1 & EP, 596028, A1	1-4, 19-25, 27/ 5, 26/ 6-18, 28-30
X/Y/A	JP, 7-327698, A (株式会社エスアールエル) 19.12月.1995 (19.12.95), (ファミリーなし)	1-4, 19-25, 27/ 5, 26/ 6-18, 28-30
P, X	WO, 97/45555, A1 (PHARMACIA BIOTECH AB) 4.12月.1997 (04.12.97), (ファミリーなし)	1-4, 19-25, 27

 C欄の続きにも文献が列挙されている。 パテントファミリーに関する別紙を参照。

## \* 引用文献のカテゴリー

「A」特に関連のある文献ではなく、一般的技術水準を示すもの

「E」先行文献ではあるが、国際出願日以後に公表されたもの

「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献(理由を付す)

「O」口頭による開示、使用、展示等に言及する文献

「P」国際出願日前で、かつ優先権の主張の基礎となる出願

の日の後に公表された文献

「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「&amp;」同一パテントファミリー文献

国際調査を完了した日

27.10.98

国際調査報告の発送日

10.11.98

国際調査機関の名称及びあて先

日本国特許庁 (ISA/JP)

郵便番号 100-8915

東京都千代田区霞が関三丁目4番3号

特許庁審査官(権限のある職員)

内田俊生

4B 8214



電話番号 03-3581-1101 内線 3448

C(続き) .	関連すると認められる文献	
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
Y	Science, Volume 263, issued 11 February 1994, Martin Chalfie et al., "Green Fluorescent Protein as a Marker for Gene Expression", pages 802-805	5, 26
A	Cold Spring Harbor Symposia on Quantitative Biology, Volume 51, issued 1986, R. M. Myers and T. Maniatis, "Recent Advances in the Development of Methods for Detecting Single-base Substitutions Associated with Human Genetic Diseases", pages 275-284	9-22
A	Genomics, Volume 14, issued 1992, A-Lien Lu and Ih-Chang Hsu, "Detection of Single DNA Base Mutations with Mismatch Repair Enzymes", pages 249-255	9-22
A	Science, Volume 236, issued 17 April 1987, Richard A. Gibbs and C. Thomas Caskey, "Identification and Localization of Mutations at the Lesch-Nyhan Locus by Ribonuclease A Cleavage", pages 303-305	9-22
Y	Proceedings of the National Academy of Sciences of the United States of America, Volume 93, issued October 1996, Mark Schena et al., "Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes", pages 10614-10619	28-30
Y	JP, 60-61594, A (ジョエル ブレスラ 外2名) 9.4月.1985 (09.04.85), (ファミリーなし)	28-30
A	JP, 9-504699, A (ジーン チェック、インク) 13.5月.1997 (13.05.97) & WO, 95/12689, A1 & EP, 733126, A1	1-30
A	WO, 95/29258, A1 (ST. JAMES' AND SEACROFT UNIVERSITY HOSPITALS NHS TRUST) 2.11月.1995 (02.11.95) & EP, 758402, A1	1-30
A	Mutation Research, Volume 374, Number 2, issued 21 March 1997, Barbara L. Parsons and Robert H. Heflich, "Evaluation of MutS as a tool for direct measurement of point mutations in genomic DNA", pages 277-285	1-30